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EXAMINER	
CHEN, STACY BROWN	
ART UNIT	**PAPER NUMBER**
1648	

DATE MAILED: 02/12/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/030,544	SCHMIDT ET AL.	
	Examiner	Art Unit	
	Stacy B Chen	1648	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *06 November 2003*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-83* is/are pending in the application.

4a) Of the above claim(s) *68-80 and 83* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-67,81 and 82* is/are rejected.

7)☒ Claim(s) *24* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *08 January 2002* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. §§ 119 and 120

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

13)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application) since a specific reference was included in the first sentence of the specification or in an Application Data Sheet. 37 CFR 1.78.

a) ☐ The translation of the foreign language provisional application has been received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121 since a specific reference was included in the first sentence of the specification or in an Application Data Sheet. 37 CFR 1.78.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

1. Applicant's election of Group I, claims 1-67 and 81-83 in the response filed November 3, 2003 is acknowledged. Because applicant did not distinctly and specifically point out the supposed errors in the restriction requirement, the election has been treated as an election without traverse (MPEP § 818.03(a)). Claims 1-83 are pending. Upon further consideration, claim 83, drawn to a vector, properly belongs in Group II with the nucleotides. Therefore, claims 68-80 and 83 are withdrawn from consideration being drawn to a non-elected invention. Claims 1-67 and 81-82 are examined.

Specification

2. The abstract of the disclosure is objected to because it contains more than the maximum limit of 150 words. Correction is required. See MPEP § 608.01(b).

Claim Objections

3. Claim 24 is objected to because of the following informalities: Claim 24 has a spelling error. Appropriate correction is required.

Claim Rejections - 35 USC § 112

4. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 58-62 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method of stimulating the immune system of an individual to induce an immune response or partially protecting against infection, does not reasonably provide enablement for inducing complete protection. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make or use the invention commensurate in scope with these claims. The breadth of the claims is unreasonable, encompassing protection against PIV, which means that an individual is partially or completely immune to PIV infection (specification, page 65, lines 1-7). The nature of the invention is drawn to vaccines against PIV. The state of the art shows that a vaccine candidate comprising a cold-passaged PIV3 is attenuated, genetically stable and immunogenic in seronegative human infants (specification, page 2, lines 16-22). A composition comprising a human-chimeric PIV3 induced a level of resistance to HPIV3 challenge in primates, and the method of producing the chimera was considered a foundation for the evaluation of candidate vaccines to protect against HPIV3-induced disease in humans (Bailly *et al.*, *J. Virology*, 2000, page 3188-3195). The level of one of ordinary skill in the art is high. The level of predictability in the art is low and the quantity of experimentation needed to make or use the invention is great, evidenced by the fact that chimeric human-bovine PIV were only candidates and served as a foundation for further evaluation according to Bailly *et al.* at the time of the present invention. The specification provides a working example performed in rhesus monkeys showing that infection with a chimeric PIV comprising a bovine PIV genome background with substituted human F and HN glycoproteins induced antibodies that reacted more efficiently with BPIV3 than HPIV3. Replication of challenge HPIV3 was significantly reduced in the upper and lower

respiratory tract of previously immunized monkeys (specification, page 86, line 20-34). This example demonstrates that the chimeric PIV has the ability to induce an immune response or provide partial protection, however, it fails to demonstrate complete protection. Therefore, given the state of the art, the breadth of the claims and the low level of predictability in the art, the claims are not enabled for full scope being claimed.

5. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claim 56 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Claim 56 recites that the chimeric PIV of claim is a virus, which appears redundant. Clarification is requested.

Claim Rejections - 35 USC § 102

6. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> (e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

Claims 1-9, 11-67 and 81-82 are rejected under 35 U.S.C. 102(e) as being anticipated by Murphy *et al.* The applied reference has some common inventors with the instant application. Based upon the earlier effective U.S. filing date of the reference, it constitutes prior art under 35

U.S.C. 102(e). This rejection under 35 U.S.C. 102(e) might be overcome either by a showing under 37 CFR 1.132 that any invention disclosed but not claimed in the reference was derived from the inventor of this application and is thus not the invention "by another," or by an appropriate showing under 37 CFR 1.131.

The claims are drawn to an isolated infectious human-bovine chimeric parainfluenza virus (PIV) comprising a major nucleocapsid protein (N), a nucleocapsid phosphoprotein (P), a large polymerase protein (L), and a partial or complete PIV background genome or antigenome of a human PIV or bovine PIV combined with one or more heterologous gene(s) or genome segment(s) or a different PIV of a different PIV to form a human-bovine chimeric PIV genome or antigenome, wherein the heterologous gene(s) or genome segment(s) encodes one or more of PIV N, P, C, D, V, M, F, HN and/or L protein(s) or fragment(s) thereof, and additionally (claim 3) wherein the heterologous gene(s) or genome segment(s) encodes a complete open reading frame of one or more of PIV N, P, C, D, V, M, F (a glycoprotein), HN and/or L protein(s). The heterologous gene(s) or genome segment(s) includes a heterologous regulatory element. The heterologous gene or genome segment is substituted for a counterpart gene or genome segment in a partial PIV background genome or antigenome. The gene or segment is added adjacent to or within a noncoding region of the partial or complete PIV background genome or antigenome. The gene or segment can also be added or substituted at a position corresponding to a wild-type gene order position of a counterpart gene or genome segment within the partial or complete PIV background genome or antigenome. Claims are also drawn to the chimeric PIV of claim 1, wherein the chimeric genome or antigenome comprises a partial or complete BPIV background genome or antigenome combined with one or more heterologous gene(s) or genome segment(s)

from a human PIV. The HPIV genes (glycoproteins HN and-or F, or a segment encoding a cytoplasmic domain, transmembrane domain, ectodomain or immunogenic epitope thereof) are substituted for one or more counterpart genes or genome segments within the BPIV background genome or antigenome. Claim 15 is drawn to a chimeric which is rBPIV3-$F_H$$HN_H$. Claims 20-23 are drawn to a chimeric PIV wherein the chimeric genome or antigenome comprises a partial or complete human PIV background genome or antigenome combined with one or more heterologous genes or genome segments from a bovine PIV, specifically the N protein or open reading frame represented by rHPIV3-N (bovine). The genome or antigenome is further modified by introduction of one or more attenuating mutations identified in a biologically derived mutant PIV or other mutant non-segmented negative stranded RNA virus, such as PIV3 JS cp45. Also claimed are specific amino acid substitutions that result in phenotypic changes and alter genes. The vector genome or antigenome is a partial or complete HPIV genome or antigenome and the heterologous pathogen is not from PIV. Also claimed is a method for stimulating the immune system comprising administering a chimeric human-bovine PIV and a physiologically acceptable carrier. Also claimed is an immunogenic composition comprising the chimeric human-bovine PIV.

7. Murphy teaches a recombinant PIV genomes and antigenomes for production of recombinant PIV comprising N, P, L, and modification to created biologically derived PIV mutants or to create chimeric human-bovine PIV (page 6, lines 9-24, and claims 1-128). The isolated, infectious PIV particles can be viral or subparticle. The particles are produced by partial or complete deletions or substitutions of non-essential genes, such as F, HN, M and C (page 7, lines 1-2). The PIV can be human (HPIV1-3), and sequences from HPIV1-3 can be

incorporated into the HPIV background genome or antigenome, such as the cytoplasmic tail and the transmembrane domain (page 7, lines 11-28). Other modifications include nucleotide insertion, rearrangement, deletion, substitution, attenuation, temperature-sensitivity, cold-adaptation, small plaque size, host range restriction, or a change in an immunogenic epitope in PIV (pages 7-8, bridging paragraph). Other recombinant PIV have multiple phenotype-specifying mutations introduced in the background genome or antigenome, such as HPIV3 JS cp45 (page 8, lines 15-28). Target genes for mutation include N, P, L, M, HN, F, C, D, and V open reading frame products (page 8, lines 29-38). Specific mutations are found on page 28, lines 6 through page 29, lines 25. Other virus' segments can be incorporated into the genome such as RSV and measles (claims 84-87 of Murphy reference). Attenuating effects can be achieved with the replacement of a human PIV coding sequence or non-coding sequence (promoter, gene-end, gene-start, intergenic or other cis-acting element) with a counterpart bovine sequence. Other mutations include ablation or reduction of expression of the C, D, or V open reading frame products (page 26, lines 1-3). Production of the chimeric PIV from cDNA is in cell or cell-free expression systems (cell-free lysate) using expression vectors (page 10, lines 27-35). Also disclosed are PIV compositions to induce an immune response against PIV using the chimeric human-bovine PIV. The composition is administered via aerosol, droplet, oral or topical route. The composition can be administered to humans in the amount of 10^3 to 10^6 plaque forming units per host (page 44, lines 5-35). Therefore, the claims are anticipated by the prior art.

8. Claims 1-9, 11-28, 30-32, 34-56 and 58 are rejected under 35 U.S.C. 102(e) as being anticipated by Belshe *et al* (5,869,036). The claims are summarized above.

Belshe teaches an isolated cp-45 hybrid virus (a derivative of HPIV-3 JS) which is suitable for use as a vaccine in humans and animals comprising nucleic acid encoding nucleocapsid protein, phosphoprotein, at least one surface antigen of a target virus, and large polymerase protein (columns 2-3). The target virus must have an envelope and one or more surface antigens or surface glycoproteins, such as HPIV-1, HPIV-2 and RSV. Belshe discloses that the gene sequence which encodes the surface glycoproteins of the target virus may be substituted for the corresponding sequence in the cp45 genome which codes for the HN and F proteins, to result in a chimeric genome (columns 8-9 and example 7). Bovine RSV and cattle HPIV-3 are typical animal viruses included within the scope of target viruses. Other viruses include RSV (F and G proteins), influenza, measles (HN and F proteins), HIV and others (col. 8, lines 42-58). Attenuating mutations are introduced into the L segment as well as other proteins (col. 5, lines 42-67 and col. 6, lines 1-3). Belshe teaches that the cp45 genome has an amino acid substitution at Leu992 in the L protein. Belshe teaches that the chimeric PIV can be used in an immunogenic composition, comprising a physiologically acceptable carrier (col. 2, lines 32-33). Therefore, the claimed invention is anticipated by Belshe.

Claim Rejections - 35 USC § 103

9. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person

having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 29, 57, 59-67 are rejected under 35 U.S.C. 103(a) as being unpatentable over Belshe *et al.* (5,869,036) as applied to claims 1-9, 11-28, 30-32 34-56 and 58 above, and further in view of Collins *et al.* (6,264,957) and Klein *et al.* (WO 93/14207). The claims are drawn to an isolated infectious human-bovine chimeric PIV wherein an attenuating mutation is stabilized by multiple nucleotide changes in a codon specifying the mutation. Also claimed is a subviral particle and the specific methods of administering the PIV to a patient. The teachings of Belshe are described above. Belshe is silent on attenuating mutations stabilized by multiple nucleotide changes in a codon and the specifics of administering the chimeric vaccine to a patient.

However, Collins teaches human-bovine chimeric RSV viral and subviral particles for immunization (column 2, last paragraph). The chimeric subviral particle comprises a recombinant RSV genome or antigenome, N, P, and L proteins (see Collins, claim 1). Both PIV and RSV are nonsegmented, single-strand, RNA viruses from the paramyxovirus family. One would have been motivated to modify the chimeric PIV of Belshe by producing subviral particles because it was well known in the art at the time of the invention that subviral particles are effective in vaccine compositions as taught by Collins. One would have had a reasonable expectation of success because Collins teaches that either viral particles or subviral particles can be used (col. 2, last paragraph).

Klein teaches a multimeric hybrid gene, comprising RSV (G or F protein) and HPIV (F or HN) protein, and combinations of these proteins such as F proteins from both PIV3 and RSV, see pages 36-37. Klein teaches a vaccine formulated for administration intranasally. One of ordinary skill would know the dosage required to elicit an immune response and would have

been motivated to make the modifications of dosage and administration in order to achieve the maximum immune response. One would also know where to add the heterologous gene segment given the well-known art of recombination and would have been motivated to incorporate the segment in such a was as to ensure its expression and stability. Belshe teaches a method of incorporating the heterologous (target gene clone) segment by ligation into the PIV clone. One of ordinary skill would have known where and how to make attenuating mutations, evidenced by Belshe which teaches that attenuating mutations are derived from the cp45 genome and virus-specific antigenic properties of the virus from which the surface glycoproteins are contributed (cols. 8-9, bridging paragraph). Stabilizing the mutation by making multiple nucleotide changes in a codon specifying the mutation is well within the capabilities of one of ordinary skill, and would have been advantageous in order to ensure expression of the mutation. Given the well known art of foreign gene expression at the time of the invention, evidenced by Belshe, Collins and Klein, the invention would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made.

Double Patenting

10. Claims 1-83 of this application conflict with claims 1-83 of Application No. 09/586,479. 37 CFR 1.78(b) provides that when two or more applications filed by the same applicant contain conflicting claims, elimination of such claims from all but one application may be required in the absence of good and sufficient reason for their retention during pendency in more than one application. Applicant is required to either cancel the conflicting claims from all but one application or maintain a clear line of demarcation between the applications. See MPEP § 822.

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. See *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970);and, *In re Thorington,* 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.130(b).

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims 1-67 provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 91, 96-117, 122-129 and 141-143 of copending Application No. 09/083,793. Although the conflicting claims are not identical, they are not patentably distinct from each other because the human-bovine chimeric instantly claimed is disclosed in the co-pending claims as a human-bovine chimeric viral particle. The instant invention claims subviral particles in addition to viruses, and therefore it would have been obvious to claim a subviral particle. This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

11. Claims 1-67 are provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 91-93, 97-100 and 102-128 of copending Application No. 09/424,628. Although the conflicting claims are not identical, they are not patentably distinct from each other because the instant invention claims subviral particles in addition to viruses, and therefore it would have been obvious to claim a subviral

particle. This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

12. Claims 1-67 are provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-4, 42, 44-50, 55-61, 74, 77-79 and 81-94 of copending Application No. 09/733,692. Although the conflicting claims are not identical, they are not patentably distinct from each other because the co-pending claims are drawn to an isolated, infectious chimeric PIV, wherein the chimera is composed of a PIV and bovine PIV portions. It would have been obvious to use a human PIV since the copending claims also claim chimerics comprising human and non-human PIV. This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

Conclusion

13. No claim is allowed.

Papers relating to this application may be submitted to Group 1600 by facsimile transmission. Papers should be faxed to Group 1600 located in Crystal Mall 1. The Fax number for Art Unit 1648 is (703) 872-9306. All Group 1600 Fax machines will be available to receive transmissions 24 hrs/day, 7 days/wk. Please note that the faxing of such papers must conform with the Notice published in the Official Gazette, 1096 OG 30, (November 15, 1989).

Any inquiry concerning this communication or earlier communications from the Examiner should be directed to Stacy B. Chen, whose telephone number is (571) 272-0896. The

Examiner can normally be reached on Monday through Friday from 7:30 AM-4:00 PM, (EST). If attempts to reach the Examiner by telephone are unsuccessful, the Examiner's Supervisor, James C. Housel, can be reached at (571) 272-0902. Any inquiry of a general nature or relating to the status of this application should be directed to the Group receptionist whose telephone number is (703) 308-0196.

SBC
Stacy B. Chen
February 3, 2004

James C. Housel 2/9/04
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